REMARKS

Upon entry of the foregoing amendment, claims 14, 16-20, and 28-36 are pending in the application, with 14, 29, and 36 being the independent claims. Claim 20 has been withdrawn by the Examiner. Claims 14 and 29 have been amended to claim the invention with more particularity. Support for the amendment to the claims is found in the specification *inter alia* at page 13, line 30 to page 14, line 6 and page 29, lines 1-21. New claim 36 has been added. Support for new claim 36 is found in the specification *inter alia* at page 13, line 30 to page 14, line 6 and page 29, lines 1-21. Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Special Status

Applicants note that this application has incurred its eighth action on the merits, and has been pending six years as of this month, surpassing the triggering events for the "special" provisions of MPEP § 707.02. Applicants are willing to work with the Examiner and the Supervisory Patent Examiner to the fullest extent possible to conclude the prosecution of the present application as expeditiously as possible.

Rejections Under 35 U.S.C. § 103

Claims 14, 16-19, and 28-35 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takesako *et al.* in view of Lenney *et al.* (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner alleges that Takesako *et al.* teaches the use of antifungal and antimicrobial agents with a fungal immunogen vaccine but does not teach a composition comprising compound 48/80. (Office Action, page 3). The Examiner further alleges that Lenney *et al.* teaches the antimicrobial activity of compound 48/80. The Examiner is of the opinion that it would have been obvious to one of ordinary skill in the art to use compound 48/80 as the antimicrobial agent in the vaccine composition of Takesako *et al.*, motivated to do so to provide antimicrobial protection to the vaccine. (Office Action, page 3). The Examiner alleges that one would have a reasonable expectation of success because the

addition of antimicrobial agents to pharmaceutical products is routinely practiced. (Office Action, page 3).

Applicants respectfully disagree. The Supreme Court has articulated that obviousness under § 103(a) is determined by an analysis of the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The obviousness or nonobviousness of the subject matter is to be determined based on these considerations however, secondary considerations such as commercial success, long-felt but unresolved needs and the failure of others can be utilized to determine the circumstances surrounding the origin of the invention. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1730 (2007). If such secondary considerations exist, they must be considered. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-1539 (Fed. Cir. 1983).

In *KSR*, the Supreme Court also made clear that predictable variations are likely obvious, but unpredictable variations are not:

> If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative - a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR at 1740.

The Court also recognized that when the prior art taught away from the claimed invention, the invention was more likely to be non-obvious: "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1996)).

The Court also emphasized the importance of identifying "a reason" that a person of ordinary skill in the relevant field would have combined the elements in the fashion claimed by the new invention. *Id.* at 1731. The Court also emphasized that this analysis should be made explicit:

> Often it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

Id. at 1740-1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The present invention is directed to a method of inducing an immune response comprising concurrently administering an immunogen and compound 48/80 to a subject in an amount effective to produce an immune response therein, wherein the compound 48/80 is administered in an adjuvant-effective amount and wherein the immunogen and the compound 48/80 are administered simultaneously in a common pharmaceutical carrier.

Takesako *et al.* is directed to fungal antigens that can be used as part of a vaccine or to suppress allergic reactions (abstract). Takesako *et al.* states that

> [t]he vaccine composition of the present invent may be used in combination with antifungal agents, such as fluconazole and amphotericin B, and β-lactam antibiotics and other various antibacterial antimicrobial agents. The vaccine composition of the present invention exhibits an additively or geometrically enhanced effectiveness when used in combination with an antifungal agent

(paragraph [0148]). Notably, Takesako *et al.* provides no working examples or other evidence to support the statement regarding an additively or geometrically enhanced effectiveness of the combination. Further, Takesako *et al.* does not mention compound 48/80, either as an antifungal agent or as an adjuvant.

Lenney *et al.* teaches that compound 48/80 has moderate antimicrobial activity against protozoa, bacteria, and fungi (Table 1). Lenney *et al.* points out that one of the least sensitive organisms tested is the fungus *Aspergillus niger* (page 703, column 2). Lenney *et al.* further points out that compound 48/80 is actually a complex mixture of polymers and that fractionation of compound 48/80 only partially separates the antimicrobial activity from the histamine-releasing activity (page 703, column 2 to page 704, column 1).

The present claims require that an adjuvant-effective amount of compound 48/80 be administered to a subject. Neither Takesako *et al.* nor Lenney *et al.* provide any teaching or suggestion that compound 48/80 has adjuvant activity. One of ordinary skill in the art reading the cited references would not be aware of any adjuvant activity and could not know that there is such a thing as an adjuvant-effective amount of compound 48/80. Thus, it could not have been obvious to the ordinary skilled artisan to carry out a method in which an adjuvant-effective amount of compound 48/80 is used.

In contrast, the present specification describes the adjuvant activity of compound 48/80 and demonstrates that administration of compound 48/80 with an immunogen produces an enhanced protective immune response relative to an immune response produced by administering the immunogen in the absence of compound 48/80. Additional evidence of the adjuvant effect of compound 48/80 is provided in the Declaration of Dr. Herman Ford Staats Under 37 C.F.R. § 1.132 filed February 21, 2008. Applicants have described a function and use of compound 48/80 that was unknown in the prior art. Thus, one of ordinary skill in the art could not have developed the claimed invention in the absence of the teachings of the present specification.

The Examiner alleges that one of ordinary skill in the art would have been motivated to add an antimicrobial agent to the vaccine of Takesako *et al.* to provide antimicrobial protection to the vaccine and that one would have had a reasonable expectation of success because the addition of antimicrobial agents to pharmaceutical products is routinely practiced. (Office Action, page 3).

Applicants respectfully disagree. While antimicrobial agents may often be present in pharmaceutical products, the cited references provide no incentive to one of ordinary skill in the art to use compound 48/80 in such a capacity. Compound 48/80 has strong mast cell degranulation activity, leading to release of histamine and resulting in inflammatory reactions (present specification, page 2, lines 4-16). Clearly, this is an activity that is not desirable for an excipient in a pharmaceutical product. Moreover, compound 48/80 is a complex mixture of unknown components, each component having unknown activities. This complexity is evidenced by the inability of Lenney *et al.* to completely separate the antimicrobial activity of compound 48/80 from the histamine-releasing activity. This lack of understanding of the

structural and functional nature of compound 48/80 is undesirable for an excipient in a pharmaceutical product. Neither Takesako *et al.* nor Lenney *et al.* provide any reason or incentive, particularly in light of the undesirable factors recited above, to select compound 48/80 as an antimicrobial agent to protect a vaccine composition, as is suggested by the Examiner.

The Examiner points to the disclosure in Takesako *et al.* regarding the combination of an antifungal agent with the fungal vaccine. However, the Examiner does not appear to rely on this disclosure to provide motivation or an expectation of success in the obviousness rejection. Instead, the Examiner appears to rely on general knowledge in the art regarding the use of antimicrobial agents to protect pharmaceutical products from contamination. As discussed above, compound 48/80 has well known undesirable properties that argue against its use in combination with a vaccine, particularly compared to other known antifungal agents mentioned in Takesako *et al.* (fluconazole and amphotericin B). Furthermore, although Takesako *et al.* states that the combination would produce additive or synergistic effects, there is no evidence presented in the reference to show that this is actually the case, thus providing little incentive to test the combination of compound 48/80 with the fungal antigen composition. Moreover, the absence of any evidence in Takesako *et al.* means that there would have been no reasonable expectation that any and all antifungal and antimicrobial agents will successfully enhance the efficacy of a fungal vaccine composition. Additionally, Lenney *et al.* teaches that compound 48/80 has only moderate antimicrobial activity against organisms in general, and that the fungus *A. niger* is one of the more resistant organisms tested. Thus, one of ordinary skill in the art would not have been motivated to use a drug that was only moderately potent and in fact was only mildly active against a major fungal organism. In the absence of any motivation or incentive to select compound 48/80 for use in combination with the fungal vaccine of Takesako *et al.*, the present claims cannot be obvious over the cited references.

The Examiner may be suggesting that it would have been obvious to try any antifungal or antimicrobial agent in combination with the fungal vaccine of Takesako *et al.* Applicants respectfully disagree. Applicants point out that the Examination Guidelines for Determining Obviousness state that even if one were to consider that the teachings of the

prior art rendered the presently claimed invention "obvious to try, " such a rationale must include 1) a finding that at the time of the invention, there had been a recognized problem or need in the art; 2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem; and 3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success (see, *e.g.*, page 57529, first column and page 57532, first through third columns).

If, for the sake of argument, one of ordinary skill in the art were to define the problem to be solved to be the selection of an effective adjuvant for use in combination with an immunogen to enhance the immune response induced by the immunogen, such an ordinary skilled artisan would have to conclude that the number of identified, predictable potential solutions to this problem, according to what the cited references provide, is not finite at all. At the time of filing of the present application, one was aware of hundreds of possible adjuvant agents. Such an ordinary skilled artisan would have to choose from an extremely large number of possible solutions in order to identify any particular agent that would solve the "problem" as described herein. It is apparent that the presently claimed compound 48/80 could not be considered to be included among "a finite number of identified, predictable, potential solutions" as set forth in the Examination Guidelines, especially as the cited references do not even indicate the possibility that compound 48/80 has adjuvant activity. Therefore the claims would not have been obvious at the time this invention was made.

If, instead, one of ordinary skill in the art reading the cited references were to define the problem to be solved to be the selection of an effective antifungal or antimicrobial agent for use in combination with a fungal vaccine to enhance the efficacy of the vaccine, such an ordinary skilled artisan would have to conclude again that the number of identified, predictable potential solutions to this problem, according to what the cited references provide, is not finite at all. At the time of filing of the present application, one was aware of hundreds, if not thousands, of possible antifungal and antimicrobial agents. Such an ordinary skilled artisan would have to choose from an extremely large number of possible solutions in order to identify any particular agent that would solve the "problem" as described herein. It is apparent that the presently claimed compound 48/80 could not be considered to be included

among "a finite number of identified, predictable, potential solutions" as set forth in the Examination Guidelines. Therefore the claims would not have been obvious at the time this invention was made. Thus, the present rejection is believed to be overcome and its withdrawal is respectfully requested.

Applicants also point to *Takeda Chemicals Industries, Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007) as relevant to the present claims. The *Takeda* court upheld a finding of non-obviousness of claims directed to a genus of chemical compounds for use in treating diabetes. In challenging the argument that the knowledge of prior art compounds and techniques rendered the claims "obvious to try," the court pointed out that "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Id.* at 1359.

Similar to the genus of chemical compounds in *Takeda*, the prior art discloses information about a large variety of antifungal and antimicrobial agents. These disclosures would result in a very broad selection of chemical structures, any one of which could have been selected for further investigation. Thus, the case law supports Applicants' position that the invention as claimed herein could not have been obvious at the time this invention was made.

It is respectfully requested that the rejection of claims 14, 16-19, and 28-35 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Accordingly, Applicant submits that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,

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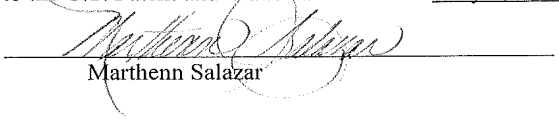
Signature: 
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